Evaluation of human exposure to the heptachlor epoxide contamination of milk in Hawaii

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The commercial milk supply on Oahu was contaminated by heptachlor epoxide for as long as 15 months during 1981-82 at levels possibly as high as 1.2 ug/g, fat basis. Following the contamination, several investigators attempted to evaluate potential adverse health outcomes, especially among infants and young children. However, results of the initial investigations are inconclusive due to lack of reliable measures of heptachlor exposure, use of non-random sampling techniques, and lack of definitive health outcomes attributable to heptachlor epoxide. The design of a current study to assess the body concentrations of heptachlor epoxide and related pesticides in Hawaii is presented. The study is designed (1) to relate these concentrations to prior exposure via the milk contamination, and (2) to assess the reliability of breast milk and serum pesticide concentrations as objective biological markers of body burden. No attempt is made to relate these data to health outcomes; instead, the findings may provide the foundation for future health studies or surveillance of environmental exposure to pesticides in Hawaii.

Introduction

Heptachlor is a chlorinated cyclodiene pesticide that has been used for > 30 years for the control of termites and soil insects. It is metabolized primarily to heptachlor epoxide, which is of comparable toxicity but more stable in biological systems[1]. Despite its long use, little information exists on the toxicity of heptachlor in humans[2]. Epidemiologic studies have been limited mostly to pesticide manufacturers or applicators[3-6], although case reports of individuals exposed to chlordane containing heptachlor have noted central nervous system toxicity[3,4,7], aplastic anemia and acute leukemia[3,4], and neuroblastoma in children with a history of pre- or post-natal exposure to chlordane[8]. Interpretation of these studies is limited due to inadequate exposure characterization, concurrent exposure to multiple pesticides, small study populations and short follow-up periods of mortality studies.

Animal studies of heptachlor have demonstrated acute central nervous system toxicity[9], subacute hepatic effects[1], and decreased fertility and gestation length with chronic feeding[7,11]. Heptachlor consumption leads to liver cancer in mice and possibly rats[3,12,13]. Given the toxicity of heptachlor in animals and the recent U.S. Environmental Protection Agency (EPA) action[14] to ban further use of heptachlor based primarily on animal studies, it is relevant to assess potential health effects in humans after instances of unintended exposure. A contamination of the milk supply on Oahu during the early 1980's represents such a case of human exposure and forms the basis of this review of earlier health studies related to the contamination. The objectives and methods of a current study to assess body concentrations of heptachlor and related pesticides in Hawaii are also presented.

Review of the contamination and initial health studies

In January 1982, the State of Hawaii Department of Health (DoH) found that the commercial milk supply on the island of Oahu was contaminated with heptachlor epoxide (HE) substantially in excess of the present Food and Drug Administration (FDA) action level of 0.1 ug/g (ppm, fat basis)[15,16]. Subsequent testing of stored samples established that the contamination may have begun in the Fall of 1980[17-19]. EPA "reasonable worse case estimates" suggested that between April 1981 and April 1982, commercial milk may have contained as much as 1.2 ug/g HE. For comparison, a surveillance program of the entire United States commercial milk supply in 1979-1982 found only 2 of 1,700 samples exceeding 0.12 ug/g HE[18].

The source of HE in the milk was chopped leaves of pineapple plants used in dairy cattle feed on Oahu[15,20]. Heptachlor was used to control ants on pineapple plants and had been used similarly for several years without incident. Due to events that remain unclear, the feed was contaminated with heptachlor probably in 1980, resulting in excretion of HE in the milk of dairy cattle. The contamination was not reported until March 1982, after which there were 11 successful milk

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recalls and monitoring of the milk supply to ensure that levels were within EPA acceptable levels.

The potentially exposed population was the entire milk-consuming population of Oahu. Milk from Oahu's 19 dairy farms (18 of which used pineapple chop for feed) was pooled at the only two processing facilities; therefore, contaminated milk was distributed throughout the island. With rare exceptions, milk produced on Oahu was consumed by Oahu residents and was not exported to the Neighbor Islands. Some speciality products, such as ice cream, were sent to the Neighbor Islands; however, the level of contamination in these products was quite low since much of the butterfat in these products came from uncontaminated sources, such as from New Zealand. Thus, contamination was limited essentially to the island of Oahu.

Earlier health studies of the contamination

Several investigators then attempted to assess whether adverse health outcomes were associated with the HE contamination. Three ecological studies, with exposure classification based on residence on Oahu during 1981-82, were undertaken to assess birth or perinatal outcomes. Two studies measured concentration of HE in human milk as an indicator of exposure. The designs of these studies are summarized in Table 1.

Burch examined trends in birth outcomes using vital records[21]. Birth, death, and fetal death certificates for 1968-1982 were examined for "fertility" and adverse birth outcomes. There was no significant change in any outcome in 1982 compared to previous years. LeMarchand et al reported the results of a temporal and geographical comparison of major congenital malformations based on hospital discharge data[22]. The investigators found that during 1970-1983, birth defects for Oahu were comparable to those for the United States, with the exception of cardiovascular malformation (CVM) and congenital hip dislocation (HD), which were significantly elevated. Because the rates of CVM and HD were elevated before 1981, the investigators concluded that the increased rates were not due to the heptachlor contamination. Grafton used medical charts to compare perinatal outcomes of births at Kapiolani Medical Center for Women and Children (KMCWC) and Tripler Army Medical Center (TAMC) during 1982 with those during 1978 and 1979[23]. There was no apparent change in birth weight, gestational age or sex ratio. An increase in jaundice during 1982 was found in some analyses, but it was not consistently significant.

The studies by Burch, LeMarchand et al and Grafton were all limited by a lack of assessment of individual exposure. Dietary studies have shown that only half of adults in Hawaii regularly drink milk[22]; thus, risk estimates based on general population rates or samples would be attenuated due to the inclusion of individuals not at risk, viz non-milk drinkers. The studies also did not evaluate the likelihood of secular trends in the outcome variables, which could have confounded the temporal comparisons. Finally, outcomes based on vital statistic reports and standard medical records may not be sufficiently sensitive to assess the effects of environmental exposures.

Siegel et al analyzed samples of human milk for HE[24]. The samples were provided primarily by donors to a breast milk bank. Figure 1 shows the HE levels found by the Siegel study compared to a survey by Takei et al in Hawaii during 1979-1980[25] and a national survey conducted by Savage et al during 1977-1983[26]. There was a significantly different distribution of high and detectable HE levels in breast milk samples after the exposure compared to earlier population samples in Hawaii, thus presenting the first evidence of increased HE levels in Hawaii's population. However, further interpretation of the study is limited since subjects were self-selected and not representative of the general population.

Table 1

INITIAL STUDIES OF HEPTACHLOR EPOXIDE EXPOSURE AND HEALTH OUTCOMES IN HAWAII

Investigator	Source of Data	Exposure Indicator	Outcome Measure
Burch (21)	Birth, death, and fetal death certificates	Residence on Oahu during contamination	Rates of adverse birth outcomes
LeMarchand, et al (22)	Hospital discharge data	Residence on Oahu during contamination	Rates of major congenital malformations
Grafton (23)	Medical charts from Kapiolani and Tripler Medical Centers	Residence on Oahu during contamination	Birth outcomes, e.g., birth weight, gestational age, or jaundice
Siegel, et al (24)	Milk specimens provided by volunteers to a breast milk program	Milk levels of heptachlor epoxide	Birth weight of children
Hoffman (26)	Milk specimens of mothers and examination of children	Milk levels of heptachlor epoxide and length of breast feeding	Birth outcomes, physical growth and behavioral development through 36 months

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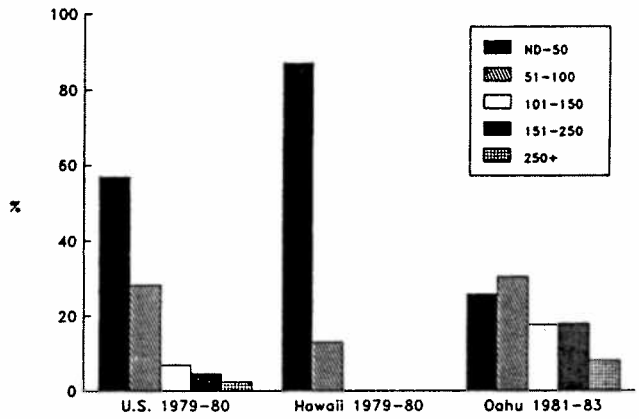

FIGURE 1 - Distributions of Heptachlor Epoxide Concentration in Breast Milk

Comparison of the distributions of heptachlor epoxide concentration in breast milk (ng/g, fat basis) found in a national survey during 1979-1980[26], in a survey in Hawaii during 1979-80 before the milk contamination episode[25], and in donors to a breast milk bank on Oahu after the milk contamination episode[24]. The last distribution is based on the first specimen provided by each subject.

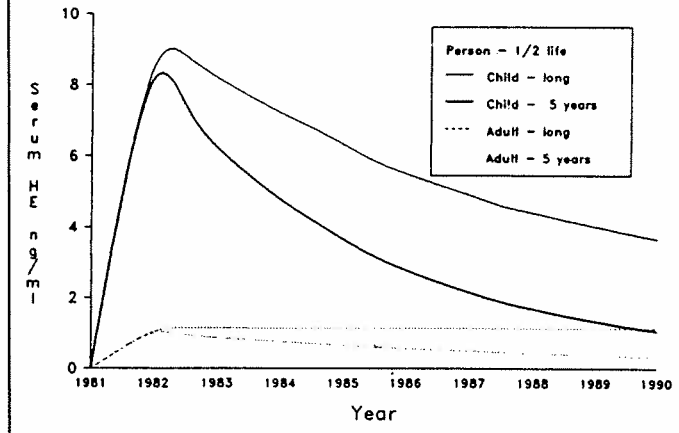

FIGURE 2 - Model of Heptachlor Epoxide Concentration in Serum

Toxicokinetic model of heptachlor epoxide concentration in the serum of an average milk-drinking adult and a child born in 1980. The model assumes that HE concentration in milk was 1.0 ug/g, fat basis, and that the contamination lasted one year. Hypothetical serum concentrations of HE are shown assuming that the half-life of HE is (a) very long or (b) five years.

One health study of children did present individual, although indirect, measures of HE exposure. Hoffman reported the results of a longitudinal evaluation of 120 infants born during 1982 potentially exposed to HE *in utero* and via breast milk[27]. Breast milk was provided by 69 mothers as a measure of exposure to the infants. The Mean HE level in breast milk was 0.123 ug/g, fat basis. Canonical correlation demonstrated a significant association between breast milk heptachlor epoxide level and infant low birth weight, gestational age, jaundice, and days in hospital after birth. Physical growth through 36 months was not associated with any exposure measure. HE level in breast milk was associated with slower acquisition of behaviors at 4 and 8 months; however, no similar detrimental effects were found at 18 and 36 months. In fact, at 18 and 36 months, duration of breastfeeding and behavioral development were positively associated. The availability of some exposure measures with longitudinal evaluation of health status and behavioral developments makes this study worthwhile, although flawed by small sample size and possibly a non-representative sample. In addition, the longer-term developmental test results were inconsistent with HE exposure and presumed continued toxicity, suggesting that the apparent detrimental effects at 4 and 8 months may not be attributable to HE exposure.

Discussion of initial studies

Results of the initial investigations of the heptachlor contamination were inconclusive due to lack of reliable measures of heptachlor exposure, use of non-random sampling techniques, and assessment of non-specific health outcomes. The studies focused on transplacental passage and human milk consumption as the critical routes of exposure. In fact, EPA estimates of HE contamination in commercial milk (1.2 ug/g, fat basis) were an order of magnitude greater than the mean level in human breast milk reported by Siegel et al (0.11 ug/g, fat basis). None of the studies assessed dose or body concentrations of HE in a representative sample of the general population. Without such information, it is not possible to define the truly exposed population, nor to evaluate the potential effect of exposure on health outcomes.

A critical issue for future health studies or surveillance of the heptachlor contamination is whether the dose was sufficient to have resulted in a biologically meaningful increment in body concentration of heptachlor epoxide. EPA estimates suggest exposure in individuals who regularly consumed the contaminated milk was substantially above that usually found in milk; however, the estimated dose was still below the "no observable effect level" in 2-year, limited dog-feeding studies, upon which the action level was based[7,19]. Thus, health outcomes due to exposure are likely to be subtle (eg developmental delay among children), subclinical (eg alterations in immune system function), or occur after long latency (eg carcinogenesis). Epidemiologic evaluation of these health outcomes is methodologically difficult, if not impossible, without use of a biological indicator of past dose at an individual level. Since HE and related pesticides are likely to persist for long periods in human tissue, it may be feasible to estimate past doses based on current human milk, serum, or adipose concentrations[28]. Such determinations could serve as objective biological markers of past exposure.

Study of body concentrations of heptachlor epoxide in Hawaii

In response to a request for proposals by the Hawaii Hep-

tachlor Research and Education Foundation[29], investigators from the Mount Sinai School of Medicine of New York in collaboration with investigators from the KMCWC and the DoH are conducting a survey to determine body concentrations of heptachlor epoxide and related pesticides in Hawaii's population. The major hypothesis is that current body concentration of HE is a reliable measure of past dose and can serve as an objective definition of exposure in Hawaii's population.

The study has two components. The first component is to determine whether concentrations of HE and related pesticides are elevated among 100 lactating women residing on Oahu compared to 50 women each on the islands of Maui and Hawaii and in the states of Arkansas and North Carolina. Women are systematically selected postpartum on the obstetric services of hospitals. They are asked to respond to a questionnaire concerning potential exposure to pesticides and to provide a specimen of breast milk to be analyzed for pesticide residues. Study hospitals include the KMCWC, Maui Memorial, Hilo County Hospital, Durham County Hospital in North Carolina, and University Hospital of the University of Arkansas for the Medical Sciences in Little Rock, Arkansas. The Analytical Laboratories of the Colorado State University will determine the levels of pesticides in the milk specimens.

The second study component is to assess concentrations of HE and related pesticides in the serum of 100 children 6 to 12 years of age residing on Oahu and 50 children each on the islands of Maui and Hawaii, and 100 adults 20 to 60 years of age on Oahu. Subjects are systematically selected from among participants in the Hawaii Health Surveillance Survey conducted by the DoH. Subjects are asked to respond to a questionnaire and to provide 7 mL of blood to be analyzed for pesticide residues. Pesticide levels will be analyzed at the Mount Sinai laboratories. Data collection for both study components began in March and continued through the Winter of 1990. Results should be available in 1991.

Discussion of pesticide body concentration study

The study should be able to determine (1) whether body concentrations of heptachlor epoxide are significantly elevated in the population on Oahu; (2) whether any observed elevation is likely due to the milk contamination; and (3) whether it is feasible to conduct an epidemiologic study of the general population or to establish a surveillance program based on assessment of individual exposure.

The breast milk study component involves human milk because it is readily accessible and sampling is noninvasive. Arkansas and North Carolina were selected as Mainland comparison areas because pesticide use is generally highest in the southeast region of the country[26]. A significant elevation of heptachlor levels in subjects on Oahu compared to subjects from the aforementioned region would indicate the need for further medical evaluation and surveillance of the physical and intellectual development of infants who are breast fed subsequent to the interval of contamination. The result will also be able to address continuing concerns about the safety of breast feeding by mothers who consumed contaminated milk.

The human serum study component utilizes blood because it is most feasible to use serum concentrations to assess body concentrations of pesticides in the general population. Adipose tissue contains higher concentrations of lipophilic pesticides; however, obtaining adipose tissue specimens is more difficult and less acceptable by the subjects under study, and it has been determined that a reliable equilibrium ratio exists between adipose tissue and serum levels[30]. Current laboratory techniques can reliably measure HE in serum as low as 0.2 ng/mL[31]. It is unlikely that changes in serum levels below the current limit of detection would be associated with significant adverse health effects, although the possibility of some biological effects cannot be ruled out since health studies have not been done.

The sampling scheme for the serum study component has been designed to determine, first, whether the age-specific pattern of body concentrations is indicative of exposure to the contaminated milk; and second, whether serum concentrations in particular are elevated. We have performed pharmacokinetic modeling based on EPA data[17-19] which suggests that children currently 9 to 11 years of age should have the greatest elevation in body concentrations of HE due to the contamination of the milk supply in 1980-82 (see Figure 2). These children — 1 to 3 years of age at the time of the contamination — would have consumed relatively large amounts of cows milk. Younger children were not as likely to have been exposed to contaminated cows' milk, and adults would have lower levels based on their larger body mass and lower milk consumption on the average. Furthermore, levels in adults would reflect longer life time exposures which could obscure elevations due to the contamination of episode per se. Thus, the sample of adults is useful in providing an estimate of the range of body concentrations in the general population, and what proportion of the population has reliably detectable serum concentration of HE. For comparison, a study based on the second National Health and Nutrition Examination Survey found that only 2.5% of the United States adult population had HE serum levels above the 1 ng/mL detection limit in that survey[32]. The current study will be able to determine whether serum HE level is a reliable quantitative measure to distinguish between exposed and unexposed populations, a crucial element for designing future surveillance or conducting etiological research.

A recent survey by the DoH found that the most pervasive public health concern of Hawaii's population is chemical pollution "due to the contamination of food and water by pesticides and other man-made chemicals[33]". This concern has arisen in part because of episodes such as the aforementioned heptachlor contamination of milk on Oahu. Such episodes present a challenge to clinical and public health practitioners to understand and interpret the risk for their patients and the public at large. The current study of heptachlor epoxide and related pesticide levels in the general population of Hawaii would contribute to our understanding of potential risk due to pesticides in the environment.

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studies and to further evaluate the mechanisms of carcinogenic action and the characteristics of exposure that lead to these effects."

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